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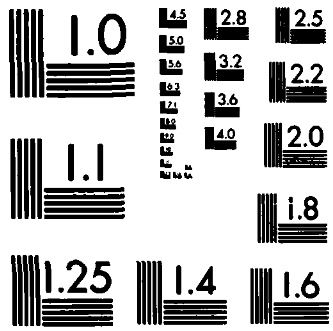

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Author(s) W.L. Daniels, J.E. Wright, J.J. Knapik, D.S. Sharp, J.A. Vogel, W.R. Beisel and G. Friman

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Nine subjects (7 experimentals, 2 controls) were studied before, during and after an experimentally induced episode of sandfly fever. During the fever, experimental subjects displayed decreases in measures of isometric muscle strength and isokinetic knee extensor strength at 36°/second. Three out of the seven subjects were unable to complete a submaximal exercise walk during the fever. Rectal temperature was elevated throughout the walk but no other physiological parameter was latered. After fever, submaximal exercise performance and muscle strength were similar to the prefever values. However, VO_2max was decreased after fever

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20. Abstract (continued)

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Experimentally Induced Sandfly Fever Virus Infection in Man: Effects on Physical Performance.

by

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ABSTRACT

Nine subjects (7 experimentals, 2 controls) were studied before, during and after an experimentally induced episode of sandfly fever. During the fever, experimental subjects displayed decreases in measures of isometric muscle strength and isokinetic knee extensor strength at 36°/second. Three out of the seven subjects were unable to complete a submaximal exercise walk during the fever. Rectal temperature was elevated throughout the walk but no other physiological parameter was altered. After fever, submaximal exercise performance and muscle strength were similar to the prefever values. However, $\dot{V}O_2$ max was decreased after fever in all subjects. This probably was related to a decrease in hematocrit caused by blood loss over the period of the study rather than a direct effect of the virus. Our results indicate that sandfly fever did diminish isometric strength during fever as well as cause a marked effect upon the ability and/or willingness of some individuals to perform exercise at gradually increasing intensity.

Infectious disease, $\dot{V}O_2$ max, Papatasi fever, isometric muscle strength, hand grip endurance.

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Decreases in various measures of physical performance have been previously reported following acute espisodes of infectious disease (2,10,14,16,20,23)or pyrogen-induced fever (19). For the most part, these studies have been retrospective; that is, patients who were hospitalized with infectious diseases were followed from the time of discharge. Studies were usually continued for several months until the physical performance measures were "normalized". While the value of such studies is unquestioned, an apparent need exists for prospective studies to support their findings. The purpose of this study was to evaluate the effect of a mild viral infection upon physical performance. Sandfly fever was selected for this study because it is an appropriate disease model for a viral infection (7,9). Sandfly fever, known medically as Phlebotomus or Papatasi fever, is a well understood, self-limiting febrile illness which is transmitted by insects of the genus Phlebotomus.

The disease is characterized by the rapid onset of flu-like symptoms. These may include headache, a generalized malaise, photophobia and aching in the muscles and joints. The most common laboratory finding is leukopenia. Anorexia, nausea and vomiting may also be associated with an ill-defined abdominal distress. The disease has a very predictable clinical course with no sequalae or complications (1,7,8,9,26-28).

For this study, subjects were evaluated before, during and after an experimentally induced episode of sandfly fever. Subjects were evaluated when the hypermetabolic effects of the fever were at their highest and during early convalescence at a time when most individuals begin to return to normal activity and when nitrogen excretion due to the protein catabolic effect of the infection is at its highest level (6).

METHODS

For this study, 9 male subjects (7 experimentals, 2 controls) volunteered to undergo a series of tests before, during and after an experimentally induced episode of sandfly fever. The experimental subjects were inoculated with plasma which had previously been shown to contain the sandfly fever virus. This plasma had been obtained, from a previous human volunteer, on the first day of illness. The control subjects were sham-inoculated with isotonic saline at the same time the experimentals received infected plasma. The overall experimental schedule for performance testing is outlined in Table 1.

Prior to testing, all subjects were given a physical exam and freely consented to participate in the study. For the pre-fever testing, subjects were divided into two groups. While one group (Group A) underwent treadmill testing, the second group (Group B) performed the muscle strength tests and vice versa. The mornings of days -4 and -2 served as introductory sessions during which subjects were familiarized with the tests that they would undergo.

Submaximal walking and muscle strength tests were performed on three occasions; before inoculation, 3 or 4 days after inoculation during the peak febrile response and on days 6 or 7 after fever had subsided. Testing began on the afternoon of days -4 and -2. All subjects underwent resting measurements which included a 12 lead electrocardiogram, body weight, blood pressure, rectal temperature (T_{re})and a pulmonary function test.

After the resting measurements, subjects began walking on a treadmill at a speed of 80.5 m/min (3 mph) and 0% grade. Every 3 minutes, the grade was increased by 3% up to a maximum of 15% grade. During the last minute at each exercise intensity, heart rate, blood pressure, rectal temperature and oxygen consumption were measured. Perceived exertion (RPE) was also assessed using the Borg scale (12).

Table 1

Experimental Schedule

Day of Week	Study Day	Test Procedure: Treadmill	Muscle Strength
Friday	-7	Screening Physical	-
Monday	-4	AM-Introduction of Procedures to Group A. PM-Sub-max Walking Group A	Group B; Isometric & Dynamic
Tuesday	-3	Running $\dot{V}O_2$ max on Group A	Group B; Handgrip
Wednesday	-2	AM-Introduction of Procedure to Group B. PM-Sub-max Walking Group B	Group A; Isometric & Dynamic
Thursday	-1	Running $\dot{V}O_2$ max on Group B	Group A; Handgrip
Friday	0	Inoculation with Plasma or Saline 0800 hours	-
Sunday	2	Hospitalization 1200 hours	
Monday	3	PM-Sub-max Walking for Febrile Subjects	AM-Isometric, Dynamic & Handgrip on Febrile Subjects
Tuesday	4	PM-Sub-max Walking for Remaining Subjects	AM-Isometric, Dynamic & Handgrip on Remaining Subjects
Thursday	6	AM-Sub-max Walking for Subjects Tested on Day 3. PM-$\dot{V}O_2$ max run	AM-Isometric, Dynamic & Handgrip on Subjects Tested on Day 3
Friday	7	AM-Sub-max Walking on Remaining Subjects. PM-$\dot{V}O_2$ max run	AM-Isometric, Dynamic & Handgrip on Remaining Subjects
		Hospital Discharge 1600 hours	

During the pre- and post-fever treadmill session, the subjects performed a maximal oxygen uptake ($\dot{V}O_2$ max) determination (22). For this test, all subjects began running at a speed of 161 m/min (6 mph) and 0% grade for 6 minutes. Following a 5-10 minute rest period, two to four additional runs were performed, each interrupted by a rest period. Exercise intensity was increased by adjusting speed and/or grade. During the last minute at each intensity, expired air was collected in Douglas bags. Subjects breathed through a mouthpiece attached to a Koegel y-valve. A plateau in oxygen consumption (increase < 2 ml/kg. min per 2.5% grade increase) was defined as $\dot{V}O_2$ max. Expired air was analyzed with a Beckman LB-2 CO_2 analyzer and an Applied Electrochemistry, Inc. S3-A 0_2 analyzer. Volumes were measured with a Tissot spirometer. No oxygen consumption data were collected on Subject 1 because he had a gagging sensation whenever he placed the mouthpiece in with a noseclip on. Therefore, data on this subject only included T_{re}, RPE and heart rate.

Muscle strength was determined for both isometric and dynamic contractions. The maximal voluntary isometric strengths (MVIS) of three muscle groups were measured using a device which has been previously described (21). The muscle groups tested were upper torso (arms and shoulders), trunk extensors and legs extensors. For the upper torso (UT), the subject was seated with the elbows set at a 90^{o} angle with the upper arms parallel to the floor. The hands grasped an overhead bar which was attached to a force transducer by a cable.

Strength of the leg extensors (LE) was assessed with the subject seated and the angle of the knees set at 90^{o}. The arches of the feet pushed against a bar attached by a cable to the transducer.

The strength of the trunk extensors (TE) was assessed with the subject in a standing position. A strap was placed around the subject's torso two inches below the acromion process. The subject extended back against the shoulder strap while driving the pelvic girdle against a stabilizing plate and the force was transmitted from the strap to a transducer.

Subjects were instructed to build up to maximal strength as rapidly as possible without jerking and to hold it until told to relax. The duration of the contractions was 3-5 seconds. Three contractions were performed on each test and the means of these were recorded as the criterion strength score.

Isometric grip strength was measured with a handgrip dynamometer which was adjusted for each subjects so as to allow maximal grip output (24,25). Subjects exerted maximal grip strength for 3-5 seconds which was transferred through a turnbuckle to a force transducer. Criterion score was the same as above. Static handgrip strength endurance time was measured by having the subject attempt to maintain 40% maximal voluntary force as long as possible using the same apparatus.

The maximal dynamic strength of the elbow flexors (EF) and knee extensors (KE) was assessed utilizing a Cybex II isokinetic dynamometer system. For EF measurements, the subject was seated and fastened by arm, leg and shoulder restraints into a heavy well-padded wooden chair which was in turn securely coupled to the isokinetic dynamometer. For KE measurements, the subject was fastened by leg and chest restraints in a separate but identical chair. Force exerted by the subject, measured as torque, was tranferred from the dynamometer via an amplifier to a PDP/1103 digital computer which measured the peak torque. Muscle strength was assessed with two individual maximal contractions for each muscle group at each of two contractile velocities, 36 and 180 degrees per second. The mean of the two contractions served as the criterion strength score.

In addition to the tests described above, subjects also had blood withdrawn daily for hematological and clinical tests. Three resting muscle biopsies were taken from the vastas lateralis of each subject prior to each treadmill walking test. Biopsies were analyzed for oxidative and glycolytic enzyme activities. The results of this portion of the study are not reported here.

The statistical analysis of the maximal oxygen consumption results was performed using a paired Student's t-test. For comparisons of data collected during the pre-fever, fever and post-fever states, an analysis of variance for repeated measures was used. Post hoc analysis was done with a Tukey's HSD test.

RESULTS

The pyrogenic effect of the virus inoculation is clearly illustrated in Figure 1. Rectal temperatures (T_{re}) began to increase about 48 hours after inoculation in the experimental subjects. Peak values for T_{re} were reached during the next 24-72 hours in all subjects. No significant changes occured in the T_{re} of the two control subjects. The experimental subjects developed the characteristic leukopenia and sympotomatology of sandfly fever (Figure 2 and Table 2). As can be seen from Table 2, there was a broad range in the severity of the the subjectives symptoms that accompanied the illness.

During fever, the heart rate and T_{re} taken at rest prior to the treadmill walk, were significantly elevated. Resting blood pressure and the pulmonary function measures were not significantly altered.

Three subjects were unable to complete the treadmill walking exercise during the fever stage. Subject 1 complained of shortness of breath, headache and dizziness. The treadmill was stopped after 30 seconds at 12% grade. Subject 5 felt dizzy after 3 minutes at 9% grade and the treadmill was stopped. Subject 6 simply stated that he could not complete the test and stopped after 1.5 minutes at 9% grade.

During the fever phase, rectal temperature was significantly elevated above pre- and post-fever values at all exercise intensities of the treadmill walk (Figure 3). However, the rate of increase in T_{re} with exercise was similar during fever to that during the pre-and post-fever state. Heart rate was significantly elevated at only the lowest intensity (0% grade) and was almost identical during all phases of testing at the three highest exercise intensities. Oxygen consumption, RPE, ventilation (BTPS) and carbon dioxide production were not significantly different during any of the testing. Ventilatory equivalent of oxygen (VEQ), however, was significantly increased at 0, 12 and 15% grade during the fever.

TABLE 2

Individual Rating of Symptoms by Subjects on Day of Testing

During Sandfly Fever

Subject	General Feeling of Illness[a]	Headache[a]	Myalgia[a]	Chills[b]	Nausea or Vomiting[b]	TOTAL
1.	4	4	2	2	2	14
2.	2	1	4	2	0	9
3.	2	2	0	2	0	6
4.	2	1	2	2	0	7
5.	3	2	1	2	0	9
6.	4	4	3	2	2	15
7.	1	0	0	0	0	1
8.	0	0	0	0	0	0c
9.	0	0	0	0	0	0[c]

a) 0 = not at all
1 = slight
2 = moderate
3 = extensive
4 = extreme

b) 2 = present
0 = absent

c) control subject

The pre- and post-fever data obtained on treadmill running performance is listed in Table 3a and 3b. At the same submaximal exercise intensity (6 mph, 0% grade), experimental subjects showed a significantly lower heart rate and oxygen consumption while there was a significant increase in ventilatory equivalent and respiratory exchange ratio after fever. At the maximal exercise intensity, experimental subjects had significantly lower heart rates, oxygen consumption and carbon dioxide production after fever as well as a significant increase in ventilatory equivalent. However, the two control subjects showed similar changes between the two test periods.

The effect of sandfly fever on muscular endurance and strength is depicted in Table 4. In the experimental group, isometric strength of the upper torso, legs and hand grip was significantly reduced during the fever trials. Isometric strength of the trunk extensors was also reduced but this was not statistically significant. Isokinetic strength of the KE was reduced at both velocities but this was only significant at the slower velocity. Isokinetic EF strength was unchanged during the course of the study. Hand grip endurance was reduced on the fever trials and this was statistically significant. Control subjects did not show any substantial changes in the strength measure except for Subject 2 who showed a reduction in TE strength and an increase in isometric hand grip endurance during the fever trials.

Table 3a

Respiratory and physiological parameters during exercise before and after fever (6 mph, 0% grade)

6 mph 0% grade

	Pre Experimentals (n=6)	Pre Controls (n=2)	Post Experimentals (n=6)	Post Controls (n=2)	p - value*
Heart Rate (bts/min)	178.5 7.2	(166) (175)	167.5 10.4	(161) (175)	0.005
$\dot{V}O_2$ (L/min)	2.87 .58	(2.76) (2.40)	2.67 .48	(2.65) (2.31)	0.05
$\dot{V}O_2$ (ml/kg min)	39.8 2.8	(41.1) (39.7)	37.1 3.6	(38.4) (37.7)	0.01
RPE	9.8 1.9	(08) (09)	9.3 1.2	(09) (12)	N.S.
$\dot{V}_E$ (BTPS)	88.3 16.5	(53.7) (67.3)	92.4 15.1	(72.1) (74.3)	N.S.
VEQ	30.9 2.3	(19.4) (28.1)	35.2 6.5	(27.2) (32.1)	0.005
R	0.99 .01	(.87) (.96)	1.03 .04	(.98) (1.01)	0.05
$\dot{V}_{CO_2}$	39.4 2.7	(35.7) (38.3)	38.5 4.6	(37.6) (38.0)	N.S.

Values expressed as mean $\pm$ SEM for experimentals.
Individual values listed for each control.
* pre vs. post for experimentals

Table 3b

Respiratory and physiological parameters during exercise before and after fever (maximal intensity)

	Pre Experimentals (n=6)	Pre Controls (n=2)	Post Experimentals (n=6)	Post Controls (n=2)	p - value*
Heart Rate (bts/min)	195.3 8.1	(189) (187)	184.7 7.9	(180) (190)	0.005
$\dot{V}O_2$ (l/min)	3.56 .46	(3.77) (2.92)	3.26 .50	(3.44) (2.88)	0.005
$\dot{V}O_2$ (ml/kg min)	50.1 4.8	(56.2) (48.3)	45.5 4.8	(49.9) (47.0)	0.005
RPE	14.8 1.0	(16) (15)	14.5 0.8	(18) (15)	N.S.
$\dot{V}_E$ (BTPS)	137.2 4.3	(117.0) (96.9)	140.2 19.9	(136.7) (113.6)	N.S.
VEQ	39.1 4.9	(31.0) (32.1)	43.4 6.6	(39.7) (34.4)	0.05
R	1.12 .06	(1.17) (1.07)	1.13 .05	(1.28) (1.11)	N.S.
$\dot{V}_{CO_2}$	56.2 6.3	(65.5) (51.6)	43.5 6.6	(63.4) (52.2)	0.005
Hematocrit	45.2 4.0	(43) (49)	38.7 3.4	(35) (39)	0.01

Values expressed as mean ± SEM for experimentals.
Individual values listed for each control.
* pre vs. post for experimentals

Table 4

Effect of Sandfly on Muscle Strength and Endurance

	Experimentals (n=7)**			Controls (n=2)***		
	Pre-Fever	Fever	Post-Fever	Pre-Fever	Fever	Post-Fever
Isometric Upper Toro (kg)	113.5 ±5.5	99.5* 10.1	108.0 7.4	101.0 125.7	100.3 117.0	101.0 127.0
Isometric Hand Grip (kg)	55.7 2.4	50.3* 2.4	53.1 2.5	48 50	53 42	54 47
Isometric Leg Extensor (kg)	204.8 19.1	156.8* 27.9	166.3 31.1	148.7 152.0	139.0 138.0	140.0 141.3
Isometric Trunk Extensor (kg)	74.4 7.3	63.0 7.8	73.9 8.5	97.3 102.7	100.7 63.3	96.0 92.3
Isokinetic Hand Grip Endurance (Sec)	142.2 17.7	101.5 13.7	138.5 5.8	108.5 160.6	114.7 220.0	105.2 204.9
Isokinetic Elbow Flexor (36° sec) (Newton-meters)	53.5 4.1	52.5 4.8	54.0 4.1	42.7 62.7	51.7 56.7	42.0 63.0
Isokinetic Elbow Flexor (180°/sec) (Newton-meters)	39.7 4.2	38.9 3.9	40.0 3.8	32.0 41.3	36.3 49.7	36.0 42.0
Isokinetic Knee Extensor (36°/sec) (Newton-meters)	227.6 16.4	184.6* 26.0	190.7 20.1	172.0 254.3	169.7 222.3	161.0 209.0
Isokinetic Knee Extensors (180°/sec) (Newton-meters)	154.3 7.8	129.3 16.0	135.9 10.4	123.3 173.7	122.3 167.3	124.3 152.0

* $p < 0.05$ (pre vs. post) ** Values expressed as $\bar{X} \pm$ SEM *** Individual values listed

DISCUSSION

In the present study, infected subjects displayed the characteristic manifestations of sandfly fever; i.e., elevated T_{re}, leukopenia, headache, myalgia and chills. Similarly, the physiological performance changes are in agreement with previous studies which showed a decrement in measures of physical performance. It must be kept in mind, however, that because of the mild nature of sandfly fever, the decrements probably were not be as severe as those seen during diseases that require hospitalization. Nevertheless, there were some marked decrements in physical performance capabilities. Among the more notable, was the fact that 3 out of 7 experimental subjects did not complete the submaximal exercise task during the fever state. This inability to perform prolonged exercise was similar to the results of Grimby (19). Grimby found that patients with pyrogen induced fever (Bacillus alkaligenes or Salmonella abortus equi) had more difficulty performing exercise of prolonged duration during the "chill" phase of fever compared to the "flush" phase or the normal condition. The "chill" phase occurs when the body temperature starts to rise suddenly and is often accompanied by shivering, nausea and headache. In the "flush" phase, the body temperature reaches a plateau and there is a general flush. Discomfort is greatest in the "chill" phase. Grimby attributed the decreased capacity for prolonged work to a reaction similar to vasodepressor syncope. However, in the present study, the subjects who stopped exercising displayed no unusual changes in heart rate and blood pressure, although two subjects said that they felt dizzy. No physiological parameter that we measured was a good indicator of the subject's ability to perform the exercise. However, the three subjects who stopped did tend to give higher values for RPE than those who completed the exercise task.

Decrements which occurred in measurements in muscle strength also support results from other studies. In the present study, muscle strength decreased between 2 and 23% during the fever. Similar results were obtained by Alluisi et al. (2) on a handgrip dynamometer in sandfly fever patients. Friman (15) also found decreases in muscle strength measurements in patients hospitalized for acute infectious diseases primarily of viral or mycoplasmic origin. Friman's patients were initially studied after they had been febrile for about one week. The results were compared to values obtained later in the convalescent period. The maximal isometric strength in these patients was decreased to 85 - 95% of their normal values. Control patients who were confined to a hospital bed for the same period of time as the fever patients did not show any significant changes in maximal isometric strength. Friman (16) also showed that isometric endurance capacity of his patients was reduced to 82.5 - 87.0% of late convalescent values in various muscle groups.

While all studies consistently show decreases in measurements of muscle strength, the mechanism of these decreases are not known. Friman et al. (18) have demonstrated abnormal transmission characteristics in the electromyographs of patients during the acute phase of disease. However, he could not correlate this with any specific measure of muscle weakness. In the present study, there were significant decreases in some measures of muscle strength but not in others. It is possible that the infection affected the recruitment of certain muscle fibers or motor units more than others. However, no electromyographic data was collected on our subjects.

Astrom et al. (3-4) have shown that during the acute phase of certain infectious diseases there were marked changes in the ultrastructure and in the activities of oxidative and glycolytic enzymes of skeletal muscle. They reported degenerative changes in myofibrils and mitochondria similar to changes seen in some types of muscular diseases. It is possible that these changes could be associated with the decreases in muscle strength. However, it is unlikely that this would be the cause of the decreases in muscle strength seen in the present study because no changes occurred in enzyme activities of skeletal muscle (Friman, personal communication). Previous studies (3) indicate that these changes may occur only in diseases of longer duration or greater severity. Therefore, even though it is well documented that muscle strength is decreased by infectious disease, the mechanism by which this is affected is not known.

$\dot{V}O_2$ max has previously been shown to decrease as a result of infectious disease. Henschel et al. (20) reported a 18.8% decrease in $\dot{V}O_2$ max in patients after experimentally induced malaria. Other investigators (10,11,14) have demonstrated reduced exercise capacity in patients after hospitalization for various infectious diseases. In the present study, the experimental subjects displayed at 8.4% decrease in $\dot{V}O_2$ max (l/min). This is similar to that reported by Friman (17) in subjects placed on bed rest for seven days. These results are complicated by the fact that in the present study, the two control subjects also showed a 8.7% and 1.4% decrease.

It appears from an analysis of the data that a decrease in hematocrit (Table 3b) seen in all subjects was a contributing factor toward the decrease in aerobic capacity. Over the time period of the present study approximately 650 ml of blood was withdrawn from each subject for various laboratory tests. However, 150 ml was the most withdrawn on any single day. While it has been demonstrated that the acute withdrawal of this amount (650 ml) will affect $\dot{V}O_2$ max (14), we did not expect the gradual withdrawal of this amount of blood to have any effect. Balke et al. (5) reported a decrease of 9% in $\dot{V}O_2$ max one hour after donation of 500 cc of blood. However, recovery of initial work capacity was achieved within 2-3 days. Ekblom et al. (13) withdrew 400 ml of blood from subjects on three occasions over an 8-day period. He found that $\dot{V}O_2$ max was reduced to 84% of control levels after the withdrawal of 1200 ml of blood. In the present study, approximately one-half (650 ml) of this amount was withdrawn from our subjects over a 14-day period. Based upon a review of the literature, we initially expected that this would have little effect on our measurements. However, the decreases in $\dot{V}O_2$ max in experimental subjects (range 2.4 - 15.8%) was similar to that seen in the two control subjects. The average decrease for all subjects was 7.55%. Therefore, these data suggest that $\dot{V}O_2$ max was decreased by the loss of blood even though blood was withdrawn in relatively small amounts over a prolonged period. It is not possible to attribute any of the decrease in $\dot{V}O_2$ max to a direct effect of the viral infection from the present data.

The decrease in HR and $\dot{V}O_2$ during submaximal running may also be associated with the blood loss. During submaximal walking, $\dot{V}O_2$ was unchanged for all intensities and conditions. However, during submaximal running in the post-fever state, $\dot{V}O_2$ was decreased by 6.8%. Similar results are reported by Ekblom et al. (13) after 1200 ml of blood loss. On a cycle ergometer, $\dot{V}O_2$ decreased by 4% at an intensity of 450 kpm/min after blood loss but was decreased by 9% at 1050-1200 kpm/min. However, they reported no change in HR whereas in the present study there was a significant decrease. The decrease in HR in the present study may be related to the fact the exercise was performed on a treadmill rather than on a cycle ergometer. However, we know of no physiological mechanism which could account for this difference. Why this would manifest itself during treadmill running but not walking is not known. However, the treadmill run was performed one day after the walk and after the last 150 ml of blood was withdrawn in the morning. This may account for this apparent discrepancy.

In conclusion, the present study demonstrates that physical performance is affected by a mild, viral infection. During the acute phase of the disease, submaximal work performance is limited in some individuals. Measurements of muscle strength were consistently decreased during the fever state. During early convalescence, submaximal exercise performance and muscle strength returned to near normal. However, the observed decrease in $\dot{V}O_2$ max was possibly due to blood loss rather than a direct effect of the virus. Our results indicate that during fever there is a marked effect upon the ability and/or willingness of some individuals to perform prolonged exercise.

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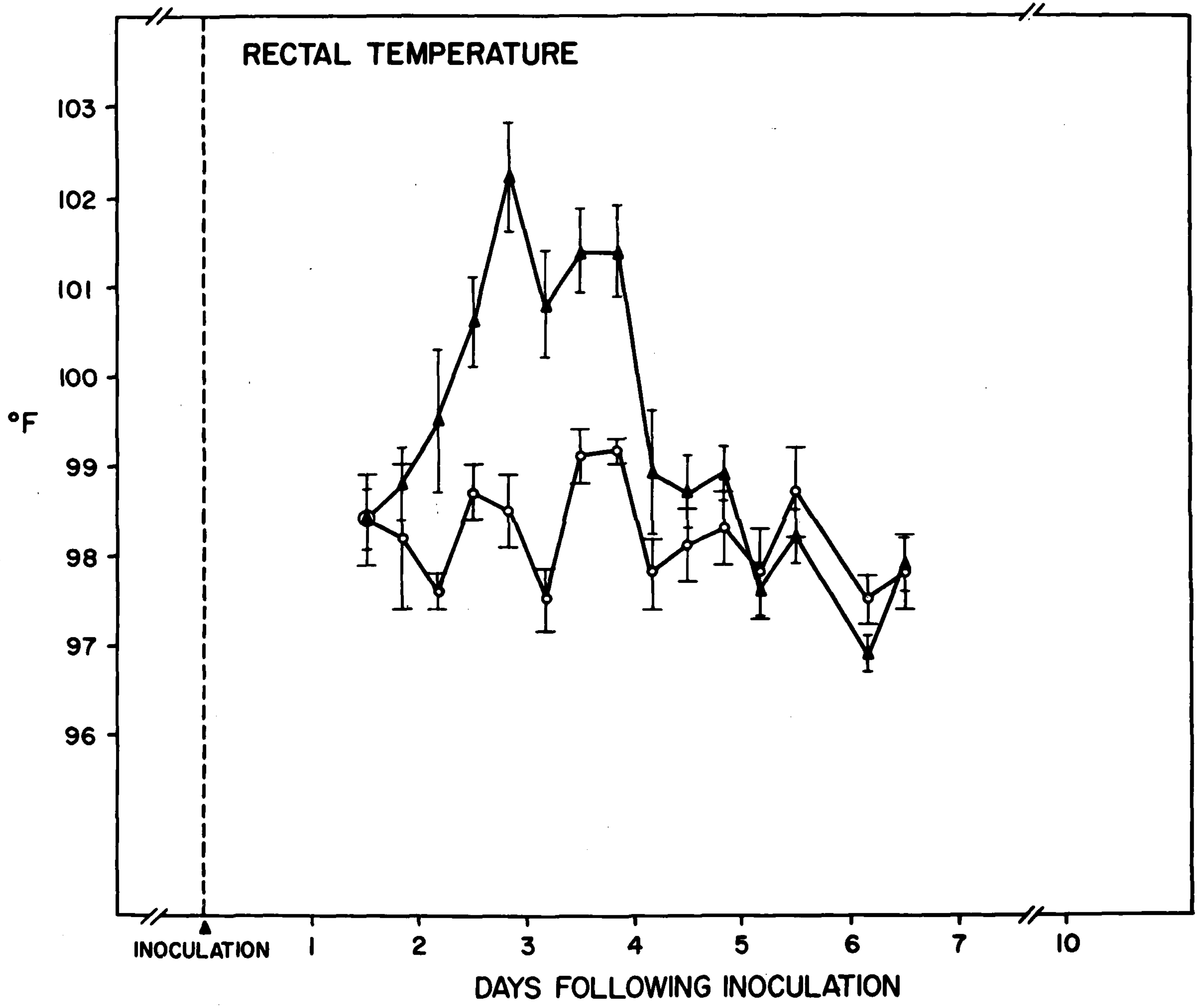
RECTAL TEMPERATURE
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103
102
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100
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INOCULATION
1
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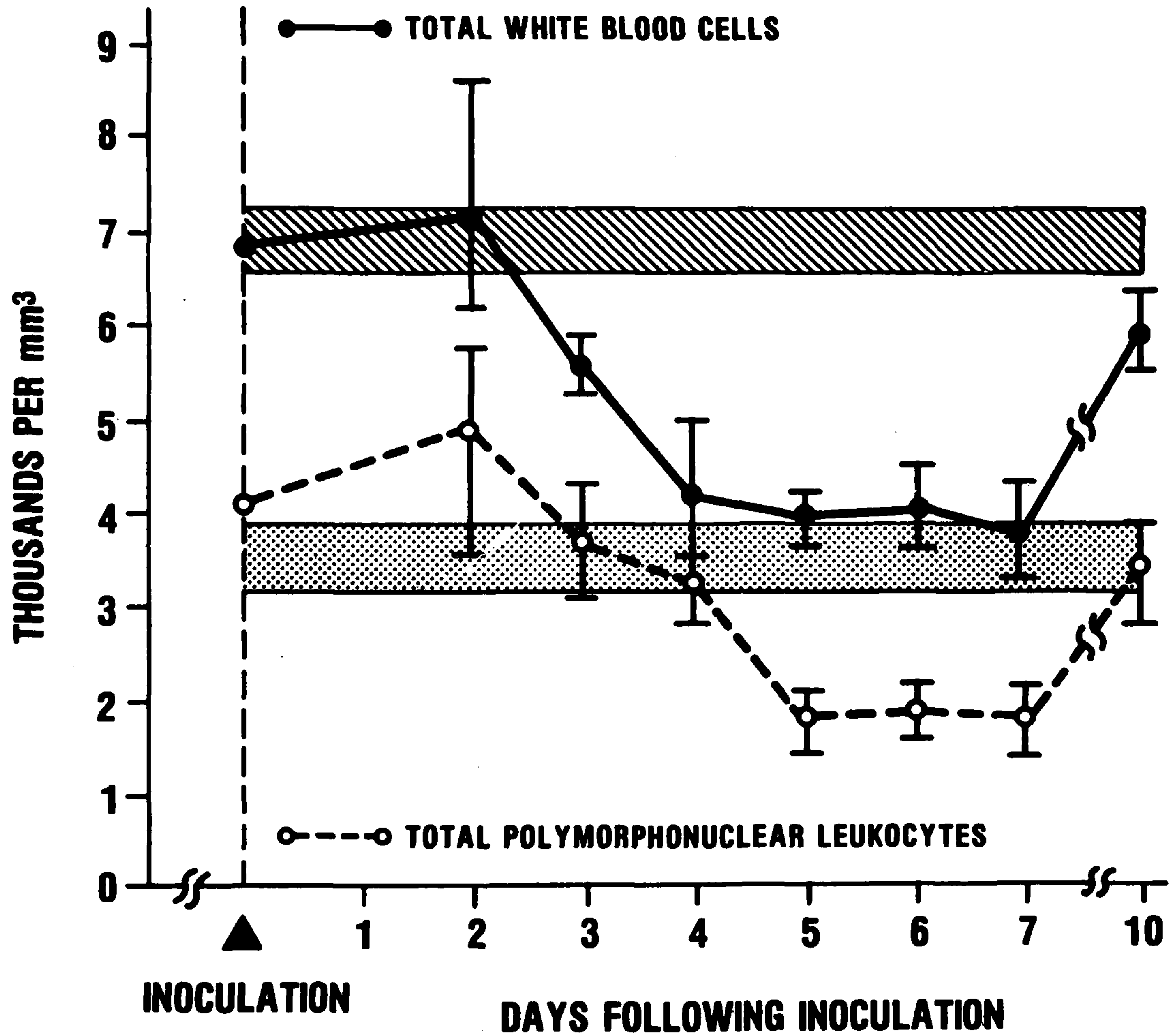
DAYS FOLLOWING INOCULATION


TOTAL WHITE BLOOD CELLS
TOTAL POLYMORPHONUCLEAR LEUKOCYTES
THOUSANDS PER mm3
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INOCULATION
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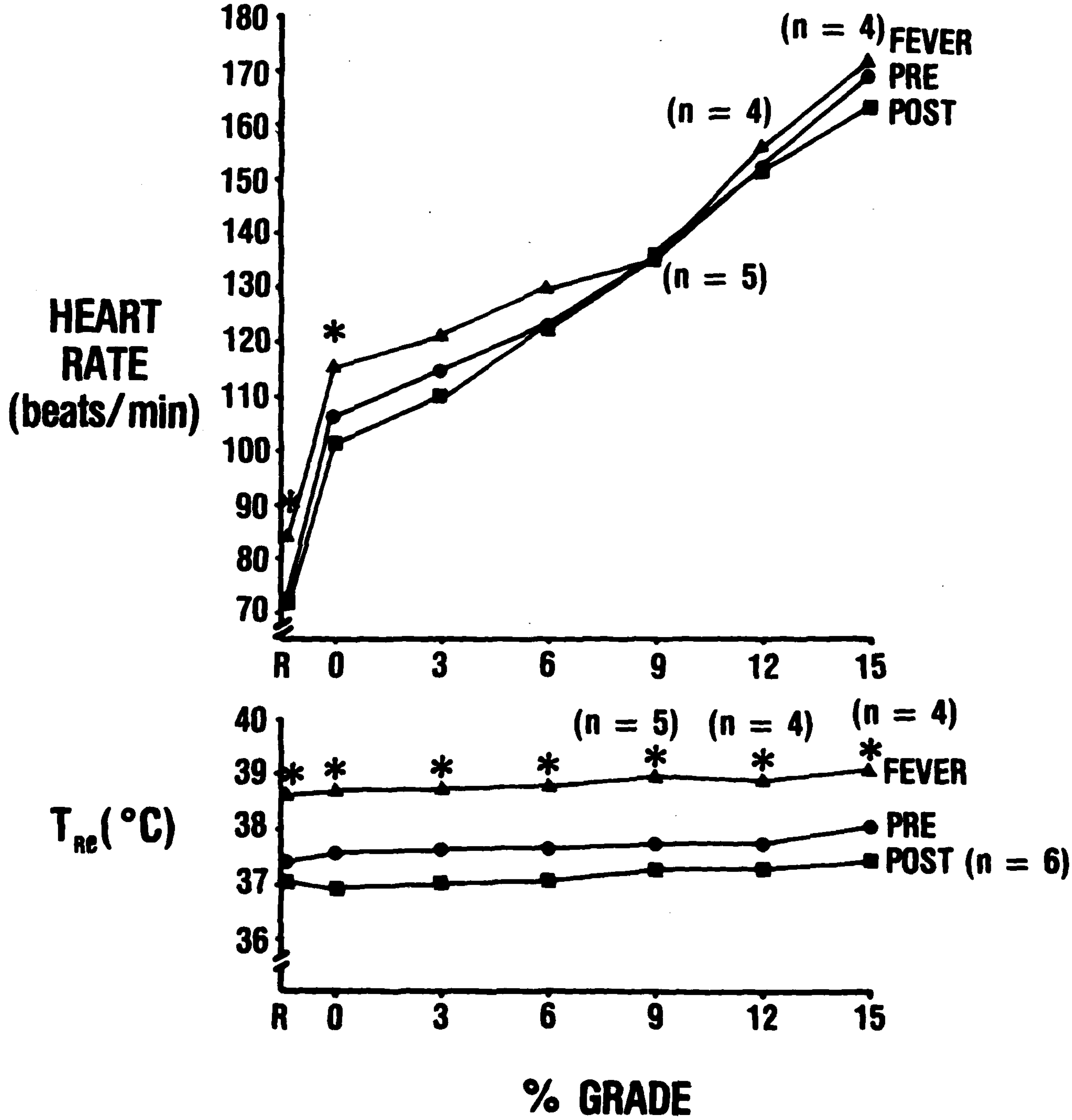
DAYS FOLLOWING INOCULATION



HEART RATE (beats/min)
180
170
160
150
140
130
120
110
100
90
80
70
(n = 4) FEVER
PRE
POST
(n = 4)
(n = 5)
*
R 0 3 6 9 12 15
T_{Re} (°C)
40
39
38
37
36
(n = 5) (n = 4) (n = 4)
FEVER
PRE
POST (n = 6)
R 0 3 6 9 12 15
% GRADE